IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	CAMPOCHIARO et al.	Atty. Ref.:	010804-22690600
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Conf. No.:	2577		
For:	OCULAR GENE THERAPY		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

A Notice of Appeal was timely filed on 14 June 2010 in the above-identified patent application. An Appeal Brief was due 14 August 2010, which is two months from the date of filing of the Notice of Appeal (37 C.F.R. 41.37(a)(1)). Attached hereto and herein incorporated by reference is a Petition, along with appropriate payment, for a five-month extension of time. With the granting of the Petition, the Appeal Brief now is due 14 January 2011. The fee for filing an Appeal Brief (37 C.F.R. 41.20(b)(2) and 41.37(a)(2)) also is submitted herewith. Accordingly, this Appeal Brief is timely filed.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real parties in interest are Wellstat Ophthalmics Corporation, a licensee of the present application, and Novartis AG, the assignee.

II. RELATED APPEALS AND INTERFERENCES

To the knowledge of the undersigned, there are no appeals, interferences or judicial proceedings that are related to, would directly affect, be affected by or have a bearing on the decision of the Board in the present appeal.

III. STATUS OF CLAIMS

Claims 4-6, 9-21, 23-26, 28-30, 32-35, 37-39 and 41-48 are cancelled.

Claims 1-3, 7, 8, 22, 27, 31, 36, 40 and 49 are rejected and are under appeal.

Claims 7, 8 and 22 are withdrawn.

IV. STATUS OF AMENDMENTS

On 21 April 2010, Applicants submitted an Amendment under 37 C.F.R. 1.116 which amended Claim 1.

The Advisory Action of 30 April 2010 indicated that the amendment of Claim 1was entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 is directed to methods for the treatment of retinal edema[1] in an individual afflicted with retinal edema, comprising effecting an increase in the amount of an endostatin[2] in ocular tissues of an individual afflicted with retinal edema to a retinal edema inhibiting effective amount, wherein the increase is effected by a subretinal injection[3] of an effective amount of a replication-defective viral vector comprising an endostatin-encoding nucleic acid[4] to the individual.

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[1] Support can be found, e.g., on page 2, lines 13-30; page 30, lines 15-29; and original Claim 1.

[2] Support can be found, e.g., on page 1, line 7 to page 2, line 12; page 10, lines 1-18; page 11, lines 9-14; page 27, line 19 to page 31, line 16; and original Claims 1-3 and 5-6.

[3] Support can be found, e.g., on page 13, lines 18-22; page 29, lines 12-15; page 29, line 31 to page 30, line 14; page 31, line 17-31; page 36, lines 4-5; original Claims 29 and 38.

[4] Support can be found, e.g., on page 1, lines 3-5; page 2, lines 1-6; page 10, lines 4-6 and 12-16; page 11, lines 9-30; page 12, lines 15-18; page 18, line 1 to page 20, line 14; page 25, line 7 to page 31, line 31; and original Claims 6-8, 17, 18, 21, 22, 29, 31-33, 36, 38, 40, 46 and 47.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection for review by the Board are whether:

(i) Claims 1-3, 27, 31 and 36 are unpatentable on the ground of nonstatutory double patenting over Claims 1-3, 27, 28, 30-32, 38-41, 45 and 51-62 of U.S. Patent Application No. 10/080,797;

(ii) Claims 1 and 31 are unpatentable on the ground of nonstatutory double patenting over Claims 52-56 and 59 of U.S. Patent Application No. 10/910,293;

(iii) Claims 1, 31, 36 and 40 are unpatentable under 35 U.S.C. 103(a) over Leboulch et al. (WO99/26480) in view of Poeschla et al. (U.S. Patent No. 6,555,107) and further in view of Brandt et al. (U.S. Patent No. 6,106,826);

(iv) Claims 1-3, 27, 31 and 49 are unpatentable under 35 U.S.C. 103(a) over Rasmussen et al. (Drug Discovery Today, 2001, 6:1170-1175);

(v) Claim 36 is unpatentable under 35 U.S.C. 103(a) over Rasmussen et al. in view of Poeschla et al.; and

(vi) Claims 1-3, 27, 31, 40 and 49 are unpatentable under 35 U.S.C. 103(a) over Rasmussen et al. in view of Nemerow et al. (U.S. Patent Application Publication No. 2002/0193327).

VII. ARGUMENT

A. Rejections on the ground of nonstatutory double patenting

(i) Claims 1-3, 27, 31 and 36

Claims 1-3, 27, 31 and 36 are rejected provisionally on the ground of nonstatutory double patenting over claims 1-3, 27, 28, 30-32, 38-41, 45 and 51-62 of U.S. Patent Application No. 10/080,797 (the '797 application).

The '797 application is no longer pending thereby rendering this particular rejection moot.

U.S. Patent Application No. 12/785,461 (the '461 application) is a continuation of the '797 application. The claims of the '461 application are essentially the same as those that were pending in the '797 application. Therefore, it might be expected that the rejection on the ground of nonstatutory double patenting would be applied by the Examiner to claims 1-3, 27, 31 and 36 of the present application over claims of the '461 application.

On indication of otherwise allowable subject matter, Applicants will consider filing a Terminal Disclaimer over the '461 application if such a rejection were lodged.

(ii) Claims 1 and 31

Claims 1 and 31 are rejected provisionally on the ground of nonstatutory double patenting over claims 52-56 and 59 of U.S. Patent Application No. 10/910,293.

However, U.S. Patent Application No. 10/910,293 is no longer pending, thereby rendering this rejection moot.

B. Rejections under 35 U.S.C. 103(a)

(i) Claims 1, 31, 36 and 40 over Leboulch et al. in view of Poeschla et al. and further in view of Brandt et al.

Claims 1, 31, 36 and 40 are rejected under 35 U.S.C. 103(a) over Leboulch et al. (PCT Publication No. WO99/26480) in view of Poeschla et al. (U.S. Patent No. 6,555,107) and further

in view of Brandt et al. (U.S. Patent No. 6,106,826) (Office Action, 14 December 2009, pages 11-19).

As discussed in detail below, the Examiner erred, inter alia,

(i) in combining Brandt et al. with the other two cited references because:

(a) the claimed invention is limited to replication-defective viral vectors and Brandt et al. explicitly teach that replication-competent viral vectors are superior to replication-defective viral vectors. Brandt et al. describe replication-defective viral vectors as being problematic with serious limitations, particularly in the area of ocular delivery (Brandt et al., column 3, lines 49-57), and/or

(b) Brandt et al. is the only cited reference that refers to subretinal injection, as recited in the instant claims. However, Brandt et al. teach that subretinal injection causes retinal detachment. One skilled in the art at the time of the invention would have wanted to avoid retinal detachment or further retinal detachment when treating retinal edema; and/or

(ii) by not making a prima facie case of obviousness because:

(a) Brandt et al. is the only cited reference alleged to relate to subretinal rejection. However, Brandt et al. specifically teach not to use replication-defective viral vectors, which are required for the claimed invention (Brandt et al., column 3, lines 49-57). Therefore, none of the cited references, including Brandt et al., teaches the claim element of subretinal rejection of a replication-defective viral vector, and/or

(b) before the presently claimed invention, those skilled in the art would not have had a reasonable expectation of success with regard to practicing the claimed invention. For example, Brandt et al. describe replication-defective viral vectors as being problematic and having serious limitations, particularly in the area of ocular delivery (Brandt et al., column 3, lines 49-57); and/or

(iii) by not giving the proper weight to the teaching away provided in Brandt et al.

Teaching Away and Cited Prior Art Do Not Teach Or Suggest All Claim Limitations

To establish prima facie obviousness of a claimed invention, an Examiner must show that all the claim elements are taught or suggested in and by the prior art (for example, *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974)).

"The examiner concedes that neither Leboulch nor Poeschla teach subretinal injection," (Office Action, 14 December 2009, page 11, line 19).

Brandt et al. mention subretinal injection only twice and, as a whole, Brandt et al. teach away from the use of subretinal injection of a replication-defective viral vector. For example, Brandt et al. stated,

> "Previous attempts to deliver a gene to various parts of the eye have used adenoviruses, adeno-associated viruses, and Herpes simplex virus. So far, researchers have only been able to 'label' retinal cells via subretinal injection, which causes retinal detachment in the area of the injection." (Brandt et al., column 4, lines 5-10)

That statement concludes that at the time, the only way to "label" retinal cells had been subretinal injection. However, that singular available means for labeling retinal cells was not without a significant side effect, namely, retinal detachment. Additionally, the "labeling" of a cell as described in Brandt et al. was done with a non-secreted protein and is therefore distinct and less complex than having a cell of the eye properly express a secreted endostatin protein from a cell transduced with a replication-defective viral vector carrying a nucleic acid encoding an endostatin as claimed.

Thus, it can be seen that Brandt et al. teach away from the claimed invention of using a replication-defective viral vector since one skilled in the art at the time of the invention would have wanted to try to avoid retinal detachment.

In an attempt to rebut that explicit teaching away, the Examiner pointed to the statement of Brandt et al., "'subretinal or intravitreal injection of a number of growth factors, cytokines and neurotrophins . . . have been shown to restore specific function to retinal or retinal pigment epithelial cells' (col. 8, lines 29-32)," (Office Action, 14 December 2009, page 12, lines 11-15).

However, the teachings of Brandt et al. concern only injection of protein and not a replication-defective viral vector.[5] Therefore, the second reference to subretinal rejection in Brandt et al. solely refers to the injection of protein and not to the injection of viral vectors, which clearly are not necessarily interchangeable and have completely different biological requirements.

For example, injection of protein avoids any potential problems and uncertainty that might have been associated with using a replication-defective viral vector to express and to secrete a protein from cells at the desired area of the eye. Delivery of protein by injection is clearly a more simple and more predictive method than attempting to express a protein from a cell and to have the expressed protein reach the diseased area in effective amounts. For example, (i) the nucleic acid of the vector must be able to enter cells in the area of the injection; (ii) the nucleic acid must travel to the appropriate cellular compartment (e.g., the nucleus) for transcription; (iii) the cells must be able to express the protein encoded by the nucleic acid; and (iv) the protein must be expressed in a manner (e.g., secretion) that allows the protein to exert an effect on the desired cells/tissue.

The retinal detachment described by Brandt et al. would have been expected to be an even larger issue for using a vector as compared to protein delivery because protein delivery does not require the retinal cells for activity, whereas the retinal cells are required to express the endostatin encoded by the viral vector as claimed. If the retinal cells were detached, such detached cells are no longer in a normal environment and may not have been "healthy" so as to enable expression of an effective amount of an endostatin. Moreover, even if the detached cells expressed and secreted the protein, the cells would have been detached from the retina and thus, possibly not in a spatial position to allow the secreted protein to reach the blood vessels responsible for the leakage/edema.

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[5] As discussed in Applicants Reply of 2 September 2009, that section of Brandt et al. refers to both Faktorovich et al. and LaVail et al. The abstracts of both Faktorovich et al. and LaVail et al. also only refer to the injection of protein and not of a viral vector.

In an attempt to address the fact that Brandt et al. teach that subretinal injection leads to retinal detachment, the Examiner stated:

> "As the 'wet' form of macular degeneration results from retinal edema and has the symptom of retinal detachment, a skilled artisan would not be concerned with the ambiguity of retinal detachment when trying to treat retinal edema in patients with macular degeneration. The skilled artisan would be more focused on inhibiting the growth of blood vessels when administering therapeutic genes by subretinal injection. (Office Action, 14 December 2009, page 12, line 18 to page 19, line 1)

Applicants respectfully disagree that a skilled artisan would not have been concerned with retinal detachment caused by a subretinal injection. The Examiner made a conclusory statement and cited no evidence to support the conclusion that, "…a skilled artisan would not be concerned with the ambiguity of retinal detachment when trying to treat retinal edema…," via subretinal injection (Office Action, 14 December 2009, page 12, lines 19-21). Also, that retinal detachment may be a symptom of a disease does not mean one skilled in the art would not have been concerned about a procedure that results in retinal detachment, which may exacerbate the disease. In fact, one of the reasons to inhibit edema is to prevent or to lessen the extent of retinal detachment.

Brandt et al. also provide a second teaching away that is unrelated to the above mentioned retinal detachment concern. The Brandt et al. reference, as a whole, describes the use of replication-competent HSV-based viral vectors in the eye. However, Brandt et al. make clear that replication-defective viral vectors are inferior, problematic and have serious limitations for ocular delivery, while a replication-competent viral vector is superior for use in the eye. For example, Brandt et al. stated:

> "Replication deficient viral vectors are frequently suggested for use in gene therapy because of safety concerns associated with using replication competent viruses. <u>The problem with replication deficient viruses</u> is that they infect one cell, and cannot propagate through a tissue or a larger area. Thus, if delivery is not efficient, only a limited number of cells are transformed. <u>This is a serious limitation, particularly in the area of neural and ocular delivery</u>, because replication is required for a virus to cross a synapse. (Brandt et al., column 3, lines 49-57, underlining added)

Since Brandt et al. refer to replication-defective viral vectors as having serious limitations, especially in the area of ocular therapy, one skilled in the art would have clearly been led away and discouraged from using a replication-defective viral vector as presently claimed. In fact, based on the teaching of Brandt et al., one skilled in the art would not have expected the claimed invention to be able to successfully inhibit retinal edema as recited in the claims. Therefore, the claimed invention cannot be considered to have been obvious at the time of the invention in light of the teaching away from the invention of interest and the lack of a reasonable expectation of success.

The Examiner referred to Brandt et al. as teaching, "'recombinant HSV vectors that express growth factors, cytokines and neurotrophins are suitable for treating ocular neuronal degenerative diseases and disorders, including ... macular degeneration' (col. 8, lines 57-60)," (Office Action, 14 December 2009, page 12, lines 16-18).

Applicants disagree that Brandt et al. "teaches" that element. On a close inspection of Brandt et al., that teaching is mere speculation. For example, there is no experimental evidence in Brandt et al. to support that position and Brandt et al. do not point to any evidence in the art to support that position. In fact, Brandt et al. contain no experimental evidence relating to using a recombinant HSV vector to express any growth factors, cytokines or neurotrophins in eye tissue, let alone via a subretinal injection, or expressing an effective amount for treatment.

In contrast, the instant specification clearly demonstrates inhibition (treatment) of retinal edema by subretinally injecting a replication-defective viral vector encoding endostatin, for instance, see Example 7. Therefore, unlike the instant specification, Brandt et al. do not demonstrate the use of any viral vectors to treat ocular diseases.

In summary, Brandt et al., as a whole, teach away from subretinally injecting a replication-defective viral vector comprising an endostatin-encoding nucleic acid. Additionally, as discussed above, Brandt et al. do not teach subretinal injection of a replication-defective viral vector as claimed and Brandt et al. teach away from the claimed invention. Neither Leboulch et al. nor Poeschla et al. cure those deficiencies or

negate the teaching away of Brandt et al. Hence, based on the cited documents, the claimed subject matter would not have been obvious at the time of invention.

No Reasonable Expectation of Success

The Examiner must show that there is a reasonable expectation of successfully combining the teachings of the references. (for example, *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Neither Leboulch et al. nor Poeschla et al. disclose subretinal injection of a replication-defective viral vector. To allegedly cure that fatal deficiency of the two primary references, the Examiner advanced the Brandt et al. reference, which makes passing mention of subretinal injection as a type of injection known in the art. However, following the guidance provided, for example, by the *In re Vaeck* (947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)) decision, the three documents can only be properly combined if on considering those documents, an artisan would have had a reasonable expectation of successfully obtaining the claimed invention.

Instead, the three cited documents do not provide a reasonable expectation of success with regard to treating retinal edema by subretinal injection to an individual of an effective amount of a replication-defective viral vector comprising an endostatin-encoding nucleic acid.

As discussed above, Brandt et al. teach away from the claimed invention for at least 2 different reasons and therefore, Brandt et al. would have caused those skilled in the art at the time of the invention not to expect success with the claimed invention. Additionally, prior to the present invention, other potential issues would have caused those skilled in the art not to have a reasonable expectation of success. Some of those issues are as follows.

It was not known at the time of the invention if subretinal injection of a replication-defective viral vector encoding endostatin would transduce a sufficient number of ocular cells to express an effective amount of endostatin. For example, as discussed above, Brandt et al. refer to problems and serious limitations relating to using replication-defective

viruses as vectors for ocular delivery. Additionally, in Mori et al.[6], an adenoviral vector expressing endostatin was used to transduce liver cells of a mouse. It was known that adenoviral vectors readily transduce a relatively large number of liver cells and thus, express high levels of a transgene. For example, Figures 1A and 1B of Mori et al. demonstrate that endostatin expressed by liver reached serum levels of 10 μg/ml and higher.

It was not known at the time of the instant invention if a subretinal injection of a replication-defective viral vector, which will typically transduce several orders of magnitude fewer cells than the i.v. injection of Mori et al., could achieve effective levels of endostatin expression to treat retinal edema.

Additionally, the results in Mori et al. were achieved with high levels of endostatin in serum. Endostatin expressed via a subretinal injection would not have been expected to achieve a significant level of endostatin in serum, let alone an effective local amount. Moreover, it was not known if the endostatin produced via subretinal injection of a replication-defective viral vector could reach the same area of the eye as did the endostatin produced from liver cells as in Mori et al. Even if some endostatin from the subretinally-injected endostatin vector reached the same area, it could not have been known if an effective amount would reach that area of the eye.

Clearly, subretinal injection of a replication-defective viral vector will transduce completely different cell types than those transduced by i.v. injection of Mori et al. It was not known at the time of the invention if cells of the eye transduced by a subretinal injection would express effective amounts of endostatin. Furthermore, it was not known: (i) if endostatin would diffuse from the endostatin-expressing cells to the local area of retinal leakage; (ii) if cells would secrete endostatin from the correct "side" of the cells since many cells of the eye are polarized; and/or (iii) if the endostatin would diffuse in the proper direction only to be "flushed away", e.g., directly into the choroid, before effective levels could be reached at the site requiring treatment.

In addition, it was not known if cells of the eye, such as the retinal pigment epithelial cells or photoreceptor cells, could express and secrete endostatin without disrupting any of the

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[6] American Journal of Pathology, (2001) 159:313-320. Cited by the Examiner in the Office Action of 2 March 2009. Copy submitted concurrently herewith.

highly specialized functions of those cells, and without causing significant pathology. It was not known (i) whether the endostatin produced by ocular cells would be functional and/or stable and (ii) if endostatin would be degraded at a slow enough rate that would allow effective local levels of endostatin for treatment of retinal edema.

The Examiner provided Poeschla et al. as allegedly teaching using lentiviral vectors and Brandt et al. as allegedly suggesting that viral vectors would be useful for treating ocular disease (Office Action, 14 December 2009, page 15, second full paragraph).

However, since the lentiviral vectors of Poeschla et al. are replication-defective[7], one skilled in the art would have been discouraged from using the replication-defective viral vectors of Poeschla et al. because Brandt et al. teach that replication-defective viruses have problems and serious limitations, particularly in the area of ocular delivery (Brandt et al., column 3, lines 49-57).

Finally, as noted above, Brandt et al., teach that subretinal injection causes retinal detachment in the area of injection (Brandt et al., column 4, lines 7-10). Prior to the claimed invention, it was not known if such detachment from injecting a replication-defective endostatin viral vector would still allow for an effective amount of endostatin to be secreted from the cells, e.g., it was not known whether a significant number of the detached cells would die or if the detached cells would be too unhealthy to secrete effective amounts of endostatin.

Based on any one of the reasons above, at the time of the invention, there would not have been a reasonable expectation of success with regard to the claimed invention. Until the present invention, those skilled in the art did not have a reasonable expectation that the claimed invention could be practiced or utilized to treat retinal edema in an individual.

Thus, for those additional reasons, the claimed invention would not have been obvious. Instead, the wholly unexpected observation that subretinal injection of a replication-defective

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[7] Poeschla et al. stated, "The vector nucleic acid is not virulent, because the nucleic acid lacks, or is defective, for one or more gene necessary for viral replication," (column 4, lines 62-64) and, "The invention embodies several safety advantages. One important safety advantage of this invention is production of the replication-defective vector entirely in human cells," (column 12, lines 59-61).

viral vector expressing endostatin can yield effective levels of endostatin in the proper site(s) in an eye to treat retinal edema speaks to the non-obviousness of the instant invention.

Accordingly, Applicants respectfully request that the Board reverse the current rejection under 35 U.S.C. 103(a).

(ii) Claims 1-3, 27, 31 and 49 over Rasmussen et al.

Claims 1-3, 27, 31 and 49 are rejected under 35 U.S.C. 103(a) over Rasmussen et al. (Drug Discovery Today, 2001, 6:1171-1175). (Office Action, 14 December 2009, pages 20-22.)

The Examiner erred, inter alia, (i) by not making a prima facie case of obviousness because Rasmussen et al. do not teach the use of endostatin for treating retinal edema, discussed in detail below, and (ii) by not considering the teaching away provided in Brandt et al., discussed in detail above.

The Examiner cited page 1171, column 2, line 22, of Rasmussen et al. as teaching, "that macular edema . . . is one of the diseases which can be treated by the methods described within the review article," (Office Action, 14 December 2009, page 20,, lines 13-15).

However, the mention of macular edema in Rasmussen et al. is in the "Introduction" section and Applicants were unable to find "edema" mentioned anywhere else in Rasmussen et al. The Rasmussen et al. reference is limited to discussing anti-angiogenic therapies and does not teach treating edema. For example, Rasmussen et al. stated in the section titled, "Anti-angiogenic gene therapy," that:

> "Preclinical proof-of-principle studies, using either recombinant adenovectors to carry the genes encoding pigment epithelium-derived factor . . . and endostatin, or recombinant adeno-associated viruses carrying the transgene encoding for angiostatin, have recently been published and demonstrated that <u>significant inhibition of neovascularization</u> in various models of AMD or DR is feasible." (Rasmussen et al., page 1172, right column, lines 29-36, footnote references omitted and underlining added.)

Since Rasmussen et al. do not teach the treatment of retinal edema, it cannot be considered to teach all of the claim elements. For that reason alone, the Examiner has not established a prima facie case of obviousness.

Additionally, the present specification describes the discovery that endostatin is capable of inhibiting retinal edema in addition to the ability to inhibit neovascularization. None of the cited documents disclose that characteristic of endostatin and therefore cannot teach the treatment of retinal edema with endostatin.

Furthermore, as discussed above, Brandt et al. teach away from the claimed invention and prior to the present invention, one skilled in the art would not have had a reasonable expectation of successfully practicing the claimed invention.

Accordingly, Applicants respectfully request that the Board reverse this rejection under 35 U.S.C. 103(a).

(iii) Claim 36 over Rasmussen et al. in view of Poeschla et al.

Claim 36 is rejected under 35 U.S.C. 103(a) over Rasmussen et al. in view of Poeschla et al. (Office Action, 14 December 2009, pages 23 and 24).

The Poeschla et al. reference was provided as allegedly teaching, "…non-primate lentivirus vectors, including Bovine Immunodeficiency Virus (BIV) vectors …," (Office Action, page 23, lines 11 and 12).

However, that does not cure the other fatal deficiencies of Rasmussen et al. as to the claimed invention, as discussed in Section VII.B.ii, pages 18 and 19 above.

Accordingly, Applicants respectfully request that the Board reverse the instant rejection under 35 U.S.C. 103(a).

(iv) Claims 1-3, 27, 31, 40 and 49 are rejected over Rasmussen et al. in view of Nemerow et al.

Claims 1-3, 27, 31, 40 and 49 are rejected under 35 U.S.C. 103(a) over Rasmussen et al. in view of Nemerow et al. (U.S. Patent Application Publication No. 2002/0193327) (Office Action, 14 December 2009, pages 25 and 26).

Nemerow et al. was provided as allegedly suggesting, "…gene therapy methods of treating retinal diseases . . . including macular edema . . . comprising subretinal injection . . . of

viral vectors having inducible promoters . . . operably linked to a therapeutic gene. Furthermore, Nemerow teaches that endostatin can inhibit angiogenesis…," (Office Action, page 25, lines 14-18, underlining in original).

However, that does not cure the remaining fatal deficiencies of Rasmussen et al. as to the invention of interest as discussed in Section VII.B.ii, pages 18 and 19 above.

Accordingly, Applicants respectfully request that the Board reverse the instant rejection under 35 U.S.C. 103(a).

VIII. CONCLUSION

Reversal of all rejections is requested respectfully.

No fee, other than the fee prescribed by 37 C.F.R. 41.20(b)(2) for filing an Appeal Brief and the extension of time fee, is believed necessary in connection with the filing of this Appeal Brief. If any additional fee is required, the Commissioner is respectfully requested to contact the undersigned so any deficiency of fees can be addressed immediately.

Respectfully submitted,

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IX. CLAIMS APPENDIX

1. (Previously presented) A method for the treatment of retinal edema in an individual afflicted with retinal edema, comprising effecting an increase in the amount of an endostatin in ocular tissues of an individual afflicted with retinal edema to a retinal edema-inhibiting effective amount, wherein the increase is effected by a subretinal injection of an effective amount of a replication-defective viral vector comprising an endostatin-encoding nucleic acid to the individual.

2. (Original) The method of claim 1 wherein the endostatin is a polypeptide with the amino acid sequence set forth in SEQ ID NO:1.

3. (Original) The method of claim 1, wherein the endostatin is a polypeptide fragment of the polypeptide with the amino acid sequence set forth in SEQ ID NO:1, a derivative of the polypeptide with the amino acid sequence set forth in SEQ ID NO:1, or a variant of the polypeptide with the amino acid sequence set forth in SEQ ID NO:1.

4-6. (Cancelled)

7. (Withdrawn, previously presented) The method of claim 1, wherein the viral vector is an adeno-associated virus vector.

8. (Withdrawn, previously presented) The method of claim 1, wherein the viral vector is an adenoviral vector.

9-21. (Cancelled)

22. (Withdrawn, original) The method of claim 8, wherein the vector is administered in an amount of from about 10^8 plaque forming units to about 10^{14} plaque forming units.

23-26. (Cancelled)

27. (Previously presented) The method of claim 1, wherein the endostatin-encoding nucleic acid has the sequence set forth in SEQ ID NO:2.

28-30. (Cancelled)

31. (Previously presented) The method according to claim 1, wherein the viral vector is a lentiviral vector.

32-35. (Cancelled)

36. (Original) The method of claim 31, wherein the lentiviral vector is a bovine immunodeficiency viral vector.

37-39. (Cancelled)

40. (Previously presented) The method of claim 1, wherein the increase is inducibly effected by the administration to the individual of a viral vector that can cause the production in the individual of an agent that will induce the expression of the endostatin-encoding nucleic acid.

41-48. (Cancelled)

49. (Previously presented) The method of claim 1, wherein the viral vector is a retroviral vector.

X. EVIDENCE APPENDIX

- Mori et al.
    - First cited in the Information Disclosure Statement filed 21 February 2006 and then subsequently cited in the Office Action of 2 March 2009.

XI. RELATED PROCEEDINGS APPENDIX

None.